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Regenerative medicine brought to life.

Scaffolding in Regenerative Medicine

- an industrial viewpoint

CIRM / RMC Webinar

September 12, 2011

Deepak Jain, PhD

SVP, Bioprocess Research & Development

Tengion Inc.

Scaffolding in Regenerative Medicine

- an industrial viewpoint

Synopsis

- Overview on Scaffolds in Regenerative Medicine
- Designing Scaffolds
- Scaffolds Applications to Neo Organs
  - Urinary system organs
  - GI organs
- Issues and Challenges
  - Product development
  - Regulatory

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Scaffolding in Regenerative Medicine
Overview

Regenerative medicine is a rapidly evolving interdisciplinary field in health care that translates fundamental knowledge in biology, chemistry and physics into materials, devices, systems and therapeutic strategies, including cell-based therapies, which augment, repair, replace or regenerate organs and tissues.*

Regenerative medicine is the "process of replacing or regenerating human cells, tissues or organs to restore or establish normal function"**.

Regenerative medicine products typically are composed of cells and/or biomaterials. Cells provide biological cues in cell therapy products. Biomaterials (scaffolding) are used to provide structural and functional cues in tissue engineering applications. Cells and biomaterials provide a combination of biology and structure in the regeneration of tissues or organs.

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** Source: ARM website*
*** Wikipedia*

Scaffolding in Regenerative Medicine
Current Paradigm

Types of Biomaterials

- Natural
- Synthetic

- Biodegradable
- Permanent

- Implantable – solid, shape and structure
- Injectable – fluid, gel

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Scaffolding in Regenerative Medicine
Natural Scaffolds

Natural Materials

- Proteins such as collagen or fibrin
- Polysaccharides like chitosan, alginate
- Glycosaminoglycans like hyaluronic acid, possibly in combination with cross linking agents
- Decellularized tissue like SIS

Challenges:

- Availability
- Removing undesirable biological contaminants
- Lot-to lot variation – Quality Control
- Decellularization, crosslinking – alteration of native properties
- Immunogenicity

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Scaffolding in Regenerative Medicine

Natural Scaffolds

Table 1: Commercially available extracellular matrix (ECM) scaffolds

Product	Source	Tissue	Company
AlloDerm	human	skin	Lifecell
AlloPatch	human	dermis	Musculoskeletal Transplant Foundation
Avaulta®, CollaMend®	porcine	dermis	BARD
Axis™ dermis	human	dermis	Mentor
CuffPatch™	porcine	SIS	Athrotek
Graft Jacket®	human	skin	Wright Medical Tech
Oasis®	porcine	SIS	Healthpoint
OrthADAPT™, DurADAPT™	equine	pericardium	Pegasus Biologicals
Permacol™	porcine	skin	Tissue Science Laboratories
Restore™	porcine	SIS	DePuy
Surgisis®, Durasis®, Stratasis®	porcine	SIS	Cook SIS
Suspend™	human	Fascia lata	Mentor
TissueMend®, Durepair®, Xenform™, SurgiMend™, PriMatrix™	Fetal bovine	skin	TEI Biosciences
Veritas®, Dura-Guard®, Vascu-Guard®, Peri-Guard®	bovine	dermis	Synovis Surgical
Xelma™	porcine	Teeth enamel	Molnlycke

Scaffolding in Regenerative Medicine

Synthetic Scaffolds

Synthetic Degradable Materials

- Polylactic acid (PLA) - degrades within the human body to form lactic acid
- Polyglycolic acid (PGA) - degradation mechanism is similar to that of PLA, but a faster rate of degradation
- Polycaprolactone (PCL) - degradation mechanism is similar to that of PLA, but a slower rate of degradation

Challenges:

- Biocompatibility issues
- Immunogenicity
- Resorption rates
- Degradation issues – toxic compounds, consistency,
- Manufacturing contaminants
- Environmental effects

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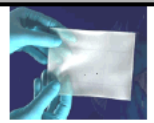
Application in Regenerative Medicine
Current Marketed Products

Product	Application	Company	Approval	
Integra Template - *silicone and bovine collagen + GAGs*	*Treatment of either a burn or scar contracture*	*Integra Life Sciences*	*1996*	
Carticel - *autologous cultured chondrocytes*	*Repair of clinically significant, symptomatic cartilaginous defects of the femoral condyle*	*Genzyme Tissue Repair*	*1997*	
Transcyte - *silicone with killed fibroblast*	*Temporary wound covering for full and partial thickness burns wounds*	*ATS/S&N*	*1997*	
Apligraf - *bio-engineered cell based product*	*Treatment of venous leg ulcers and diabetic foot ulcers*	*Organogenesis*	*1998*	
Dermagraft - *fibroblasts, placed on a dissolvable mesh*	*Wound closure of diabetic foot ulcers*	*ATS/S&N* *Now: Advanced BioHealing*	*2001*	
Infuse - *rhBMP-2 along with a carrier/ scaffold*	*Bone growth in specific, targeted areas of the spine*	*Medtronic Sofamor Danek*	*2002*	
GEM 21S - *growth factor enhanced matrix*	*Treatment of patients who have bone defects due to periodontal disease*	*Biomimetics Pharmaceuticals Incorporated*	*2006*	

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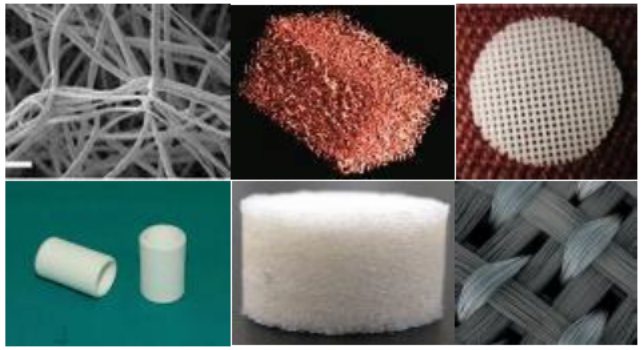
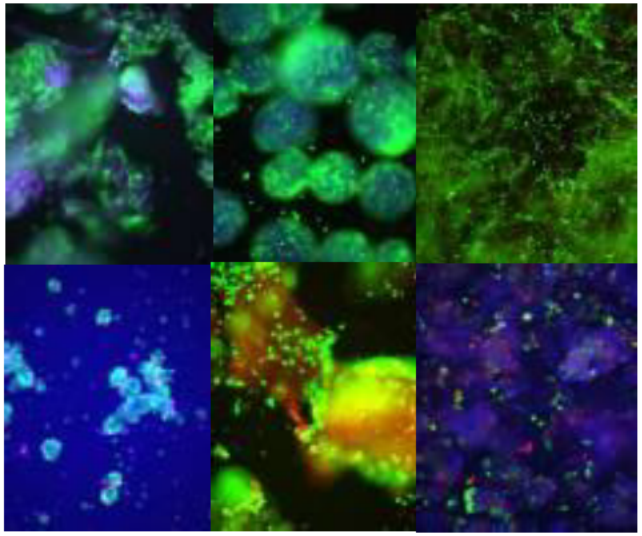
Scaffolding in Regenerative Medicine
Biomaterial Requirements

Role of Biomaterials

- *Shelf Life – extended shelf life for ABI*
- *Stability - durability during transport*
- *Safety - predictable and persistent targeted delivery of cells*
- *Support – material for cell attachment*
- *Structure - architecture for cell interactions*
- *Space – displacement of tissue*





Challenges:

- Targeting delivery without compromising distribution of active ingredients (cells)
- Providing structure without compromising compatibility

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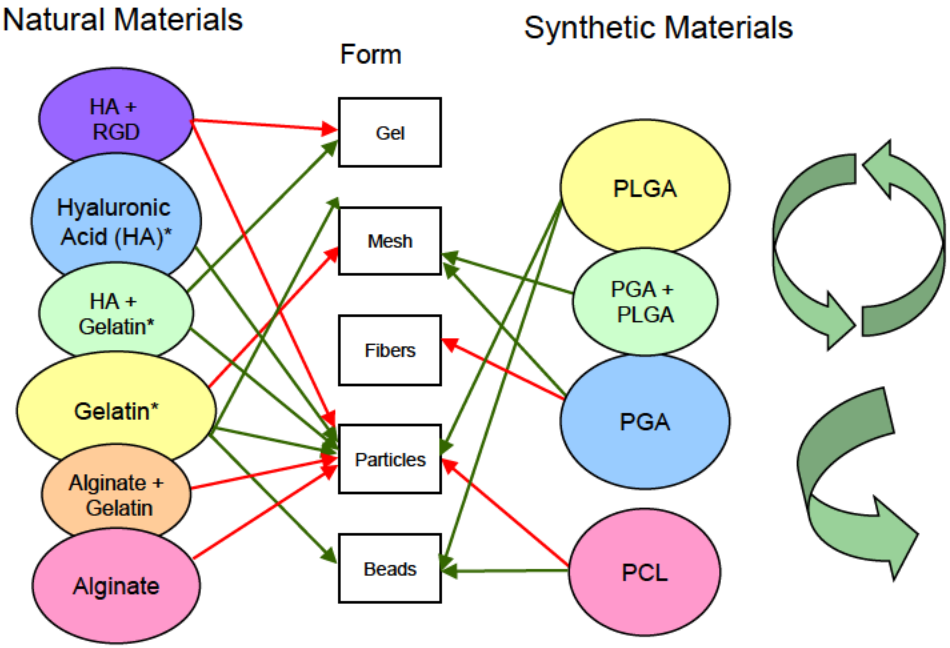
Scaffolding in Regenerative Medicine
Biomaterials: design criteria and selection

Key Criteria for Biomaterial Selection:

- *Biocompatible*
  - *Minimal Inflammatory response*
  - *Minimal fibrotic response*
  - *Facilitate neo-vascularization*
- *Bioresorbable*

Screen formulated candidates:

- In vitro
- In vivo



Cell-biomaterial formulations optimized in combinatorial screening platform

Challenges:

- Finding approved biomaterials that meet design criteria
- Regulatory hurdles in using new biomaterials

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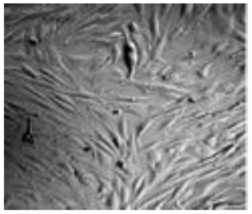
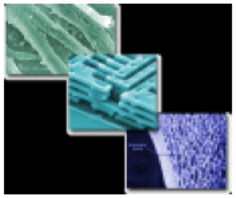
Building Neo-Organs and Neo-Tissues
Key Components

A platform that catalyzes human tissue and organ regeneration



Cells

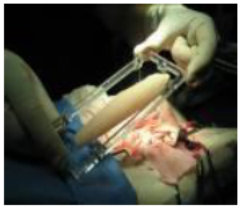


Biomaterials

INTEGRATED PLATFORM

Bioprocess/ Industrialization

Implantation/ Post-implantation



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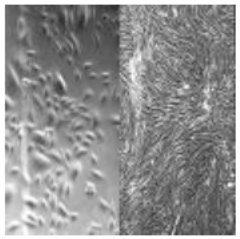
Technology Platform Yields Unique Products
Neo-Organs

Cell Source

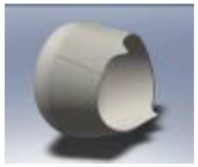
Progenitor cell(s)

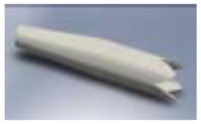
Various cells and sources used



Biomaterial

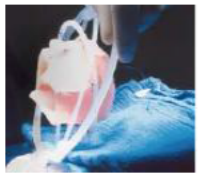
Synthetic or Natural



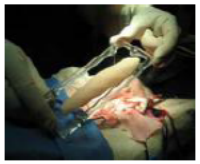


Proprietary

Products



Neo-Bladder Augment

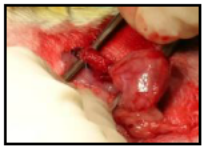


Neo-Urinary Conduit

Neo-Bladder Replacement

Neo-Vessel

Neo-Kidney Augment



Neo-GI

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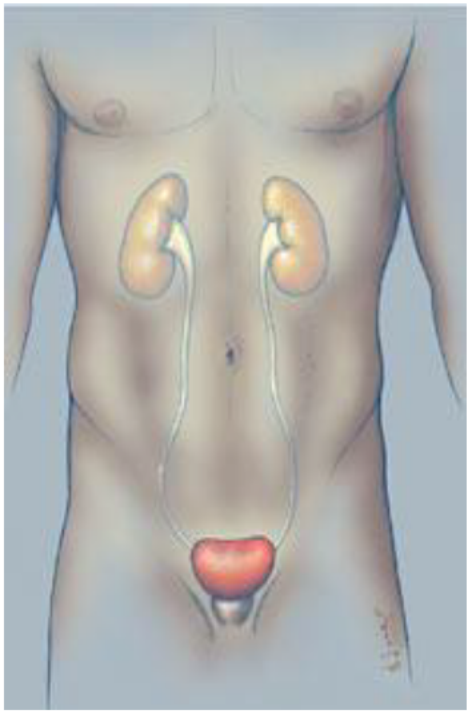
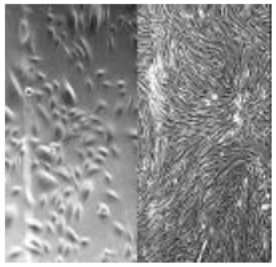
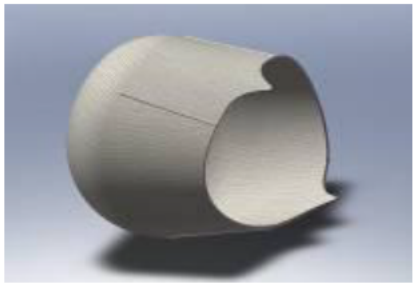
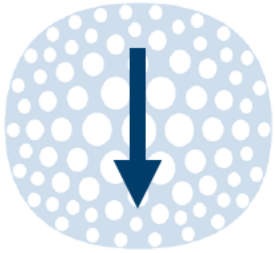
Regenerating Urinary System Organs
Neo-Bladder Augment (NBA)

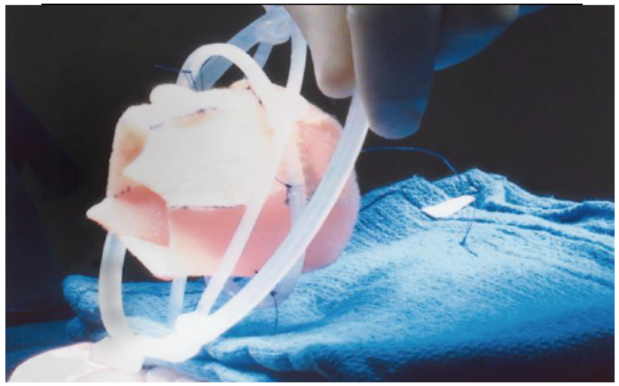


Surgeon sends patient's biopsy to Tengion.









Surgeon implants the neo-organ which regenerates and becomes functional.

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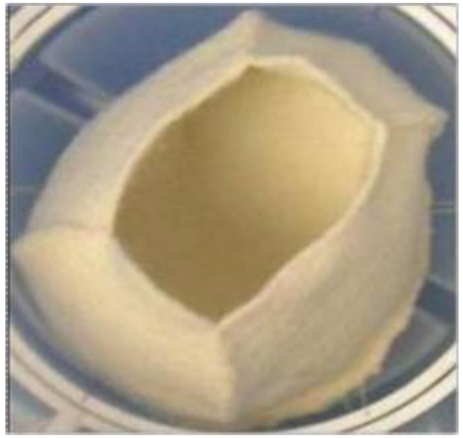
Neo-Bladder Augment
Biomaterials: scaffolds

The NBA scaffold is made up of the following:

- Polyglycolic acid (PGA) polymer mesh fashioned into a bladder shape
- Formed scaffold coated with 50:50 poly-DL-lactide-co-glycolide (PLGA) copolymer



The NBA scaffold is seeded with autologous smooth muscle cells and urothelial cells to form the NBA construct for implantation

Challenges:

- Preventing hydrolytic degradation of PGA during manufacturing
- Matching degradation rate of PGA scaffolds with tissue regeneration in vivo
- Localized toxicity of degradation product (lactic acid)

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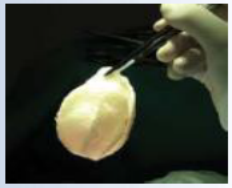
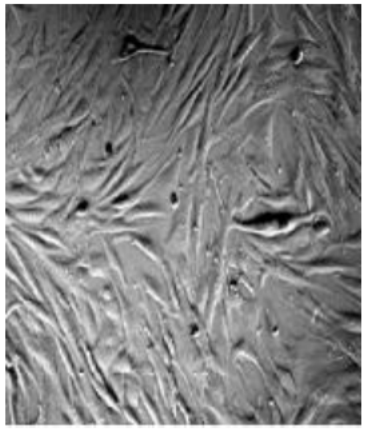
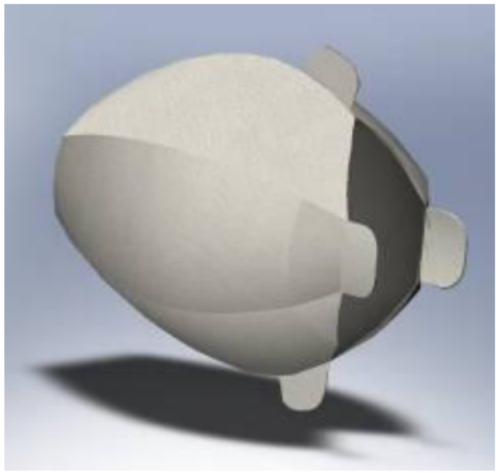
Augmentation to Organ Replacement
Neo-Bladder Replacement (NBR)



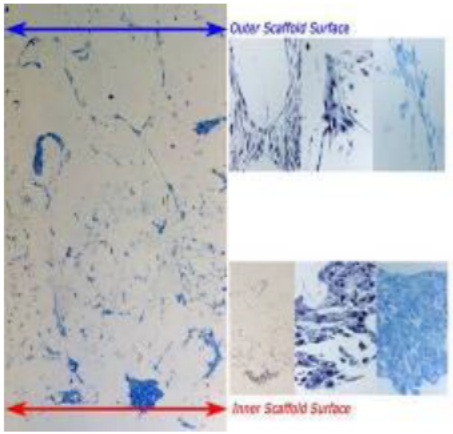
Precursor Cells



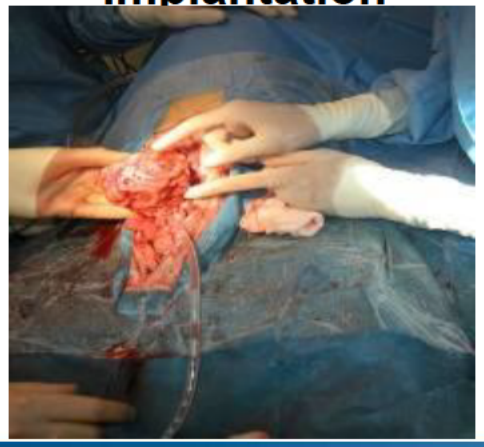
PGA Scaffold



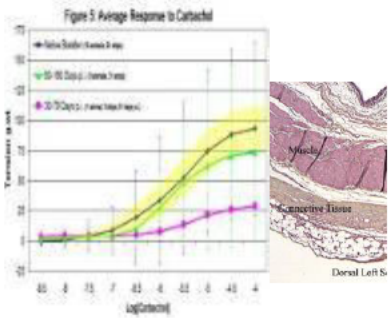
Seeded Construct



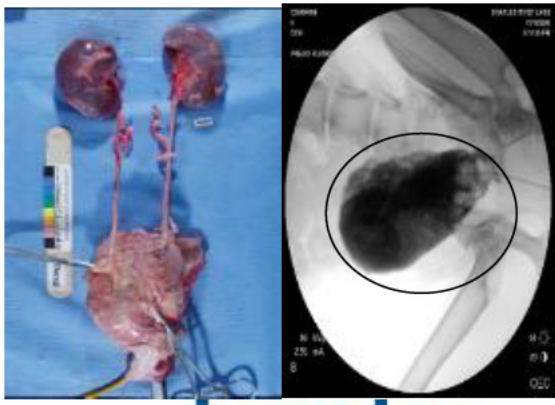
Surgical Implantation



In-situ "neo-bladder" Regeneration



Neo-Bladder



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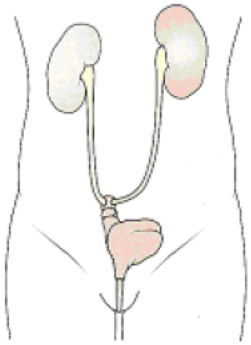
Bladder Cancer Management
Urinary diversion procedures

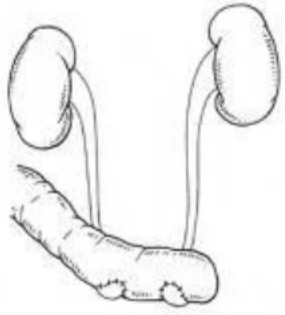
When bladder removal is needed, a urinary diversion procedure is performed…

Orthotopic Neo-bladder (1,600 annually in the US & EU)



- *Native bladder removed*
- *Section of bowel isolated, with blood supply maintained*
- *Bowel continuity re-established without the removed segment*
- *Isolated bowel segment fashioned into a pouch*
- *Ureters connected to the bowel segment, which is connected to urethra*

Non-continent Urinary Diversion Conduit (20,000 annually in the US & EU)



- *Native bladder removed*
- *Section of bowel isolated, with blood supply maintained*
- *Bowel continuity re-established without the removed segment*
- *Ureters connected to the bowel segment, which is connected to abdominal wall for ostomy bag drainage*

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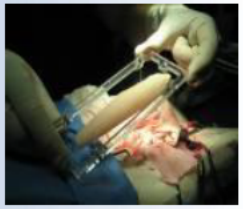
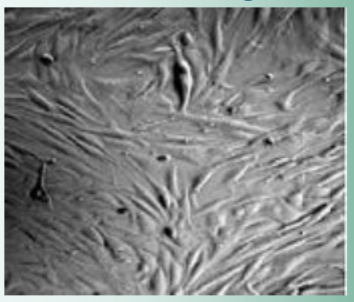
Neo-Urinary Conduit

Bladder Cancer Management - without Bowel Resection

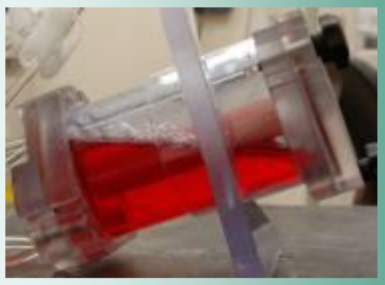


Isolation / Expansion



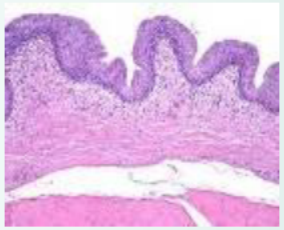
Scaffold

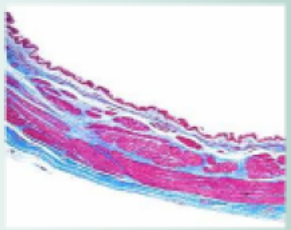
Seeding / Growth



Implantation

Functional Regeneration





- Cells and construct catalyze new tissue growth
- Blood vessels and nerves grow into the neo-organ
- Scaffold is absorbed

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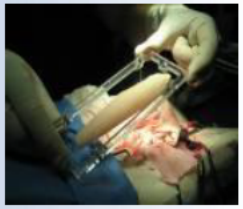
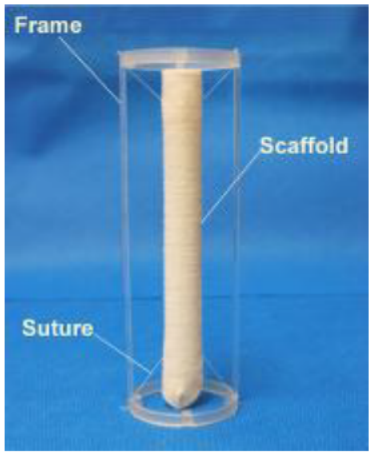
Neo-Urinary Conduit
Biomaterials: scaffolds



The NUC scaffold is made up of the following:

- Polyglycolic acid (PGA) polymer mesh fashioned into a tubular shape
- Formed PGA tube coated with 50:50 poly-DL-lactide-co-glycolide (PLGA) copolymer



The NUC scaffold is seeded with autologous smooth muscle cells sourced from adipose tissue to form the NUC construct for implantation

Challenges:

- Preventing hydrolytic degradation of PGA during manufacturing
- Maintaining compressive strength PGA tubular scaffolds with tissue regeneration in vivo
- Surgical technique

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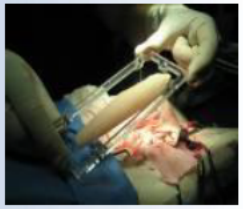
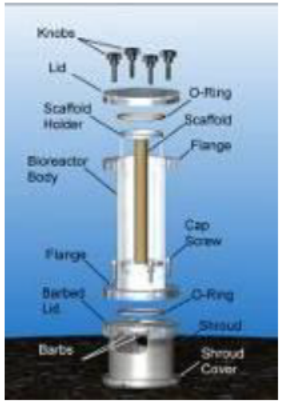
Neo-Urinary Conduit
Bioreactor/Construct Manufacturing



Bioreactor:

- *Design input from clinical and regulatory*
- *Biocompatible product contact materials*
  - *USP Class VI grade polycarbonate*
- *Provide an environment for cell seeding, SMC growth and construct maturation*
- *Closed system for aseptic manufacturing*
- *Maintain integrity during transport (air and ground)*
- *User-friendly handling of the NUC at the surgical site*



Construct:

- *Cells are harvested and seeded on scaffold in bioreactor*
- *Cell-seeded scaffold is matured into a NUC construct in the bioreactor*

Challenges:

- Biocompatible clinical-grade materials
- Designing a aseptically sealed bioreactor that can be easily opened in the OR
- Maintaining multiple quality systems for devices and biologics

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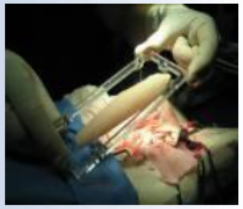
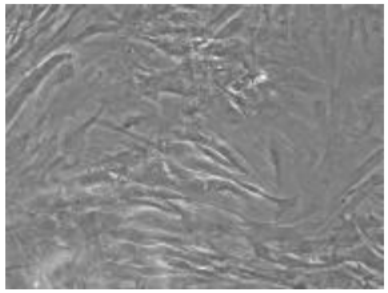
Neo-Urinary Conduit
Product Characterization

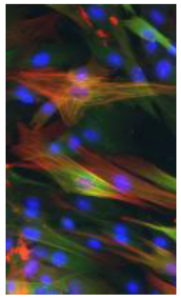


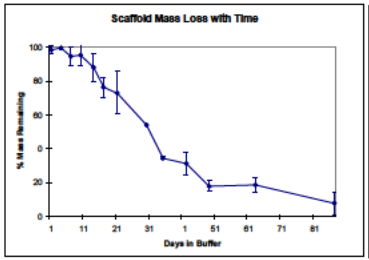
- *Cells*
  - *Morphology*
  - *Phenotype*
  - *Gene expression*
  - *Ability to contract*
- *Biomaterial/Scaffold*
  - *Physical dimensions*
  - *Pore size*
  - *Degradation rate*
  - *Tensile strength/compressive strength*
  - *Biocompatibility*
- *Construct*
  - *Cell Phenotype*
  - *Metabolic Activity*
  - *Cell Function*
  - *Secretome Profile*
  - *ECM Production*

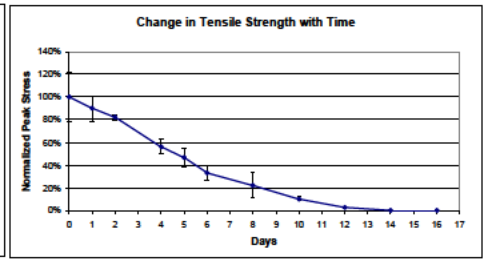
Challenge:

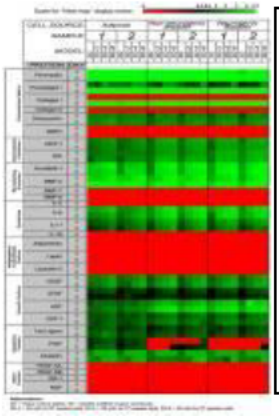
- Characterization vs Release testing

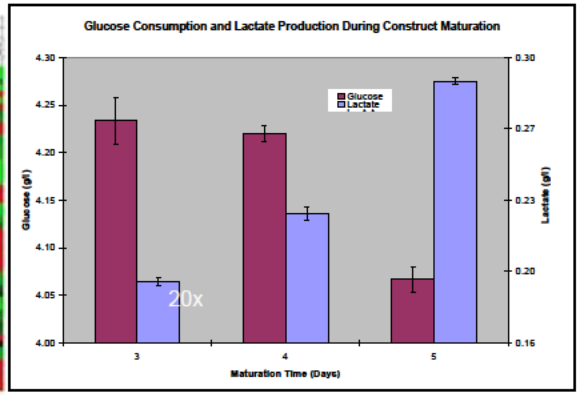












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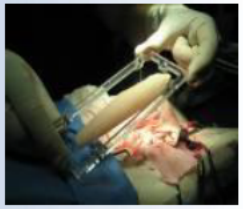
Regulatory Pathway - Combination Product
NUC



Neo-Urinary Conduit: Bladder cancer patients requiring bladder removal

- *BLA with CBER in the lead and CDRH collaborating*
- *Pre-IND discussions in advance of GLP studies*
- *IND accepted in 30 days*
- *Neo-Bladder Augment experience in US and Europe was instructive for conduit*

Key Steps in IND Development of NUC:

CMC

- **Cells**
  - Isolation, Characterization and Expansion (ICE) process
- **Biomaterials**
  - Formation, Strength and Integrity of tubular structure
- **Bioreactor**
  - Closed system bioreactor and user friendly design
- **Construct**
  - Closed seeding, cell attachment and environment
- **Transport and Delivery System**
  - Construct integrity during transport
  - Surgeon-friendly at clinical site
- **Stability**
  - Optimum shelf life and stability of product
- **Characterization & Release Criteria**
  - Cell, biomaterial and construct characterization assays and validated methods
  - Defined release criteria

Preclinical

- **Pre-GLP studies**
- **GLP studies**

Challenges:

- Release testing of lot of one (autologous)
- Defining potency of regenerative medicine products
- Non-diseased animal models

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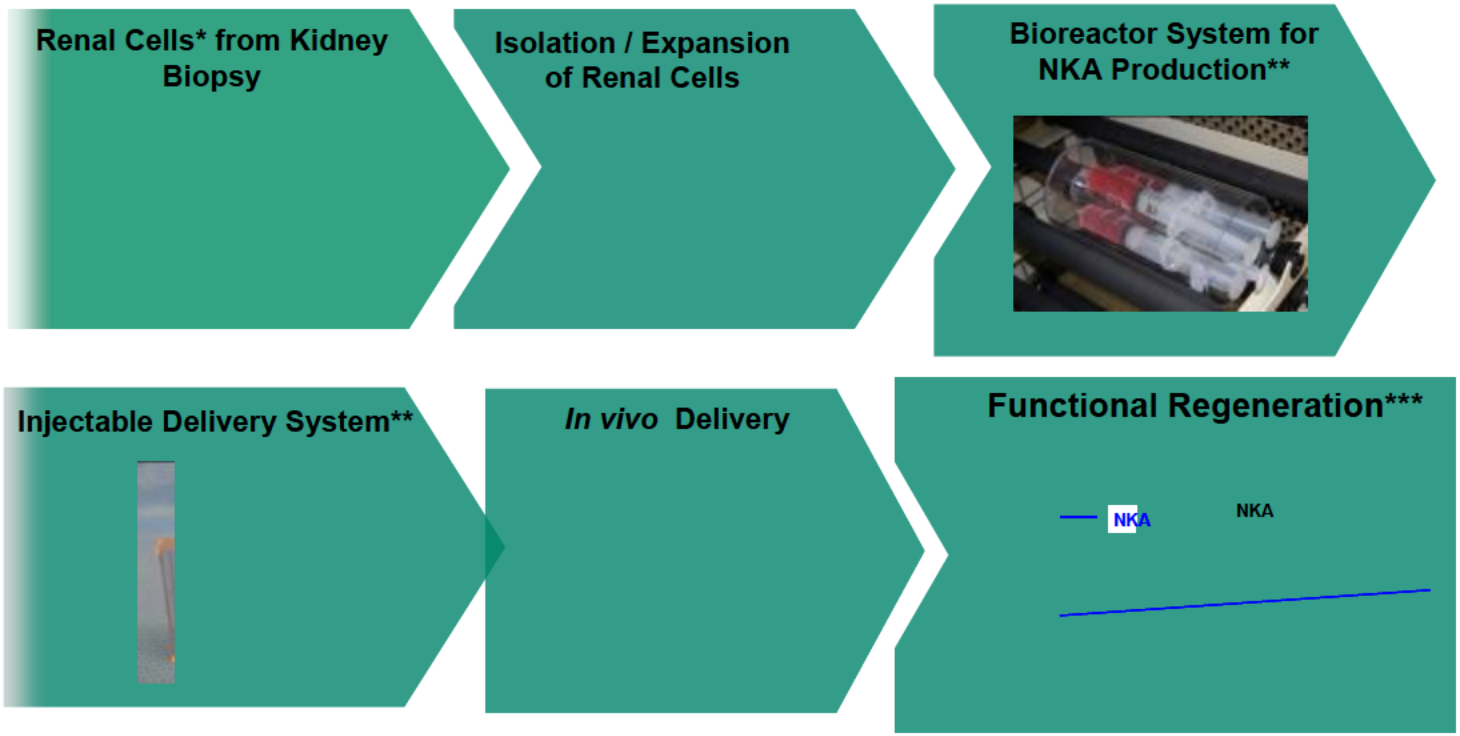
Neo-Kidney Augment (NKA)
- to delay the need for dialysis or transplantation

100,000 new dialysis patients each year in the US

- *350,000 currently on dialysis*
- *20% annual mortality*
- *$60,000 1st year cost per patient*
- *$22 billion in direct US costs annually for end stage kidney disease*



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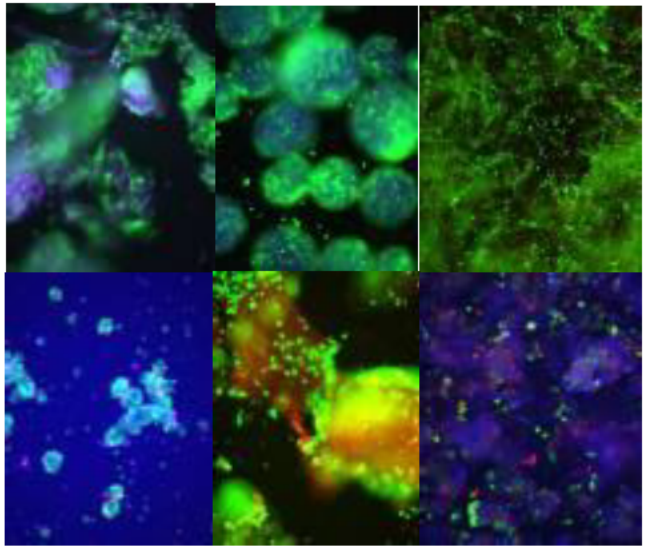
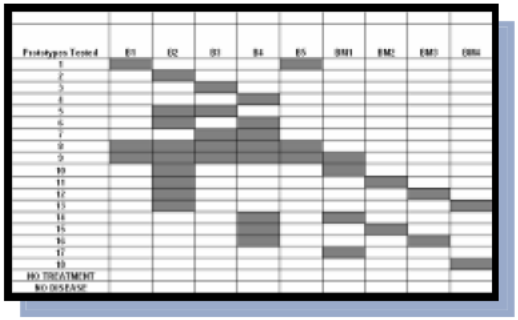
*Selected Regenerative Cells used in the NKA
** In development

***Kelley et al, Am J Physiol Renal Physiol 2010 (Published online 9/6/2010)

Neo-Kidney Augment
Biomaterials: product formulations

Renal Cell - Biomaterial Formulations





Cell-biomaterial formulations optimized in combinatorial screening platform

Challenges:

- Targeting delivery without compromising distribution of active ingredient (cells)
- Providing formulations without compromising compatibility

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Regulatory Pathway - Combination Product
NKA

Neo-Kidney Augment: Chronic kidney disease

- *Early FDA interactions*
- *Combination product development pathway*
- *Discussions in advance of Pre-IND submission*
- *Use previous development experience*

Challenges:

- Release testing of lot of one (autologous)
- Defining potency of NKA
- Non-diseased large animal models

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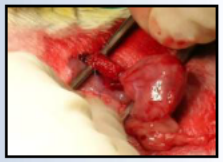
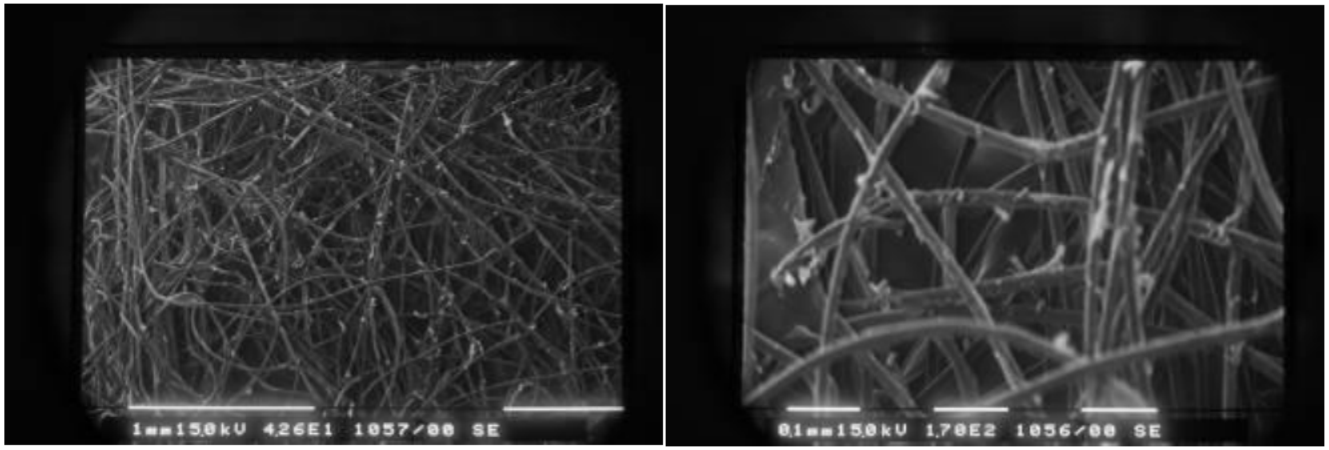
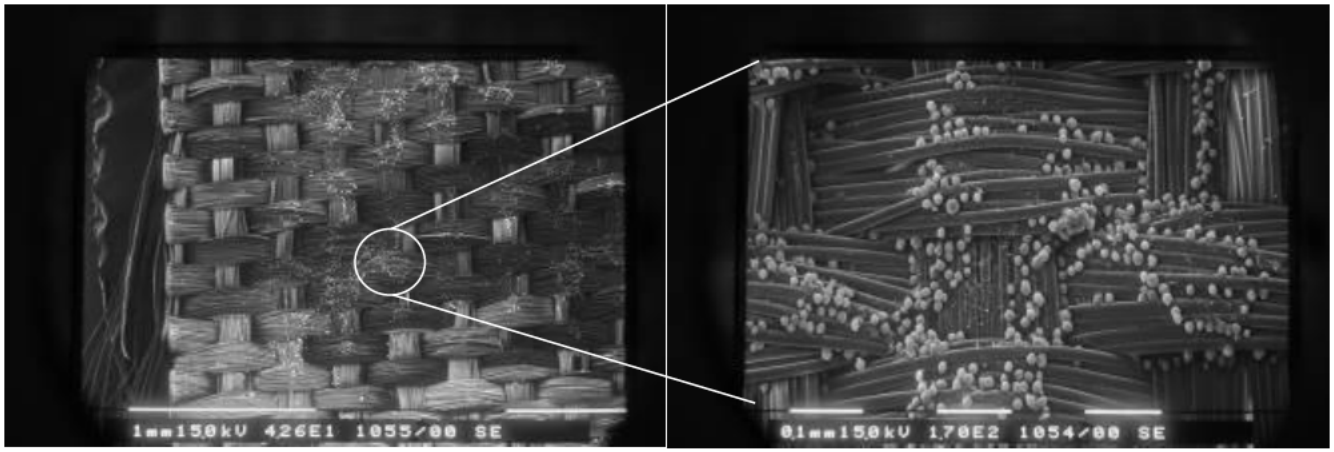
Regenerating GI System Organs
Neo-GI Esophagus



Esophageal patch: Coated PLGA mesh seeded with Ad-SMC



SI patch: Woven PLGA mesh seeded with Ad-SMC



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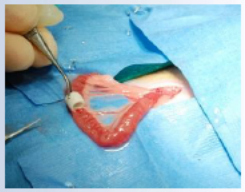
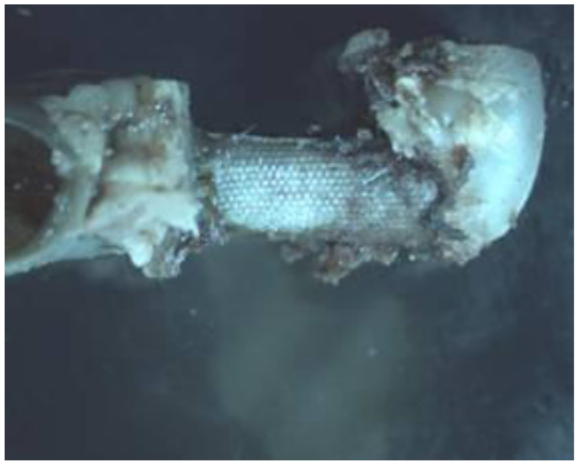
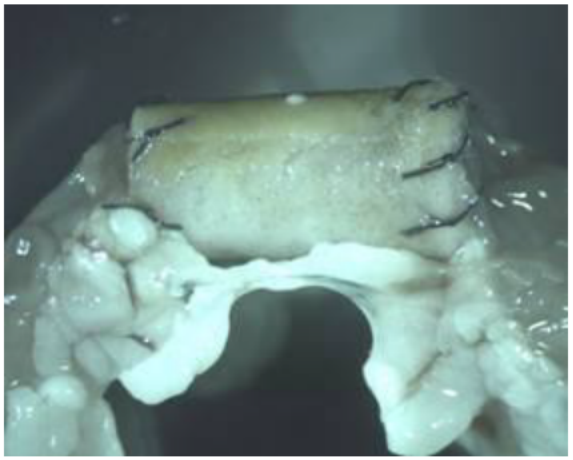
Neo-GI : Small Intestine
- *Tubular Scaffolds*



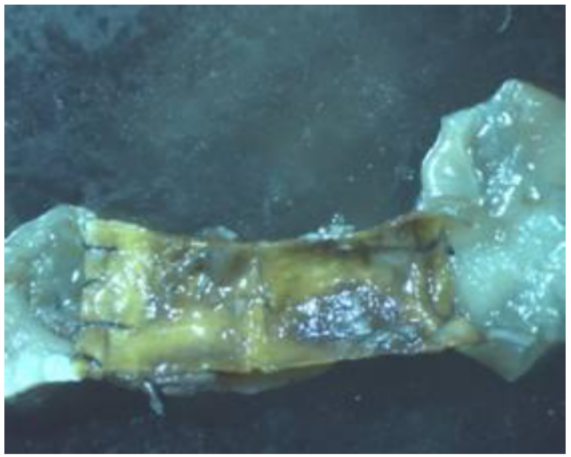
SI Tube: Coated PLGA mesh

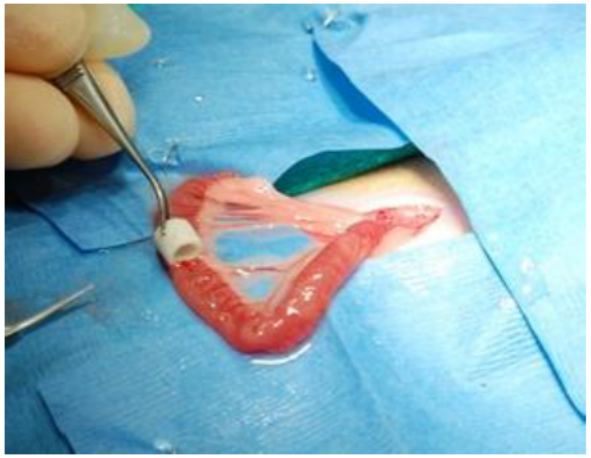


SI Tube: PCL Foam-Mesh



SI Tube: PCL Electrospun





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Scaffolding in Regenerative Medicine
- Summary

Scaffolding in Regenerative Medicine

- *Biomaterials are a key element in the development of Regenerative Medicine Products*
- *Scaffolds have been shown to be effective in creating Neo-organs and Neo-tissues*

Key Issues and Challenges

- Biomaterials/Scaffold Selection
- Manufacturing Scaffolds
- Regulatory issues

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Regenerative medicine
brought to life.